REMARKS

Applicants request consideration of the Remarks herein. Claims 19–27 are pending herein. Claim 19 has been amended. Applicants submit the amendments are supported throughout the specification including at page 6, lines 1-10. Claim 29 is new and is supported throughout the specification including at page 6, lines 20-29.

Applicants thank the Examiner for entry of the previous Amendment and withdrawal of the objection to the specification, and withdrawal of the rejections based on 35 U.S.C. § 112, first paragraph, and § 112, second paragraph.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claim 19 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Specifically, the Examiner indicates that the term "scaffold comprising first and second opposite strands" in claim 19, as previously amended, is not supported in the specification as filed. Applicants traverse this rejection.

As an initial matter, Applicants note there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *See* Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, first paragraph "Written Description Requirement" IIA. Furthermore, the written description requirement may be satisfied through sufficient description of a representative number of species, by reduction to practice, by disclosure of relevant identifying characteristics such as structure, physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of these characteristics. *MPEP 2163 II. A.3.(a)ii)*. When the above factors are carefully weighed, the specification clearly describes the claimed subject matter in a manner reasonably conveying to one of skill in the art that Applicants had possession of the claimed invention.

Claim 19, as amended, recites a scaffold, which is described in the present specification as "an amino acid framework useful for presenting a peptide of interest, in a way that the peptide of interest is accessible to other molecules" (*see* page 9, lines 1–5). The scaffold acts as a scaffold for β-turn display, where β-turn refers to an antiparallel β-sheet structure comprising a turn region and two opposite strands with defined tertiary structure (*see* page 9, lines 6–8).

Furthermore, the scaffold is described as comprising at least two Trp-Trp non-hydrogen bonded cross-strands, which provide a zipper-like motif, thereby stabilizing the β-hairpin structures. The scaffold is therefore clearly comprised of opposite strands that form the tryptophan zipper (or trpzip) motif.

In light of the above remarks, the specification clearly describes the claimed subject matter in a manner reasonably conveying to one of skill in the art that Applicants had possession of the invention. The written description requirement has been met, and Applicants request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 19–27 under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse this rejection.

The Examiner suggests that it is unclear how the plurality of peptides having the recited properties are formed by a single step method. Applicants point out that the synthesis of the peptides is described extensively in the present Application. For example, the construction of the library by phage display is described in the specification, at page 11, line 26 to page 13, line 2. Similarly, the preparation of a variety of different peptides is described in the Examples (*see* Example 1, pp. 25–30).

The Examiner questions whether the scaffold comprises a first and second opposite strand, or whether each strand is the presented turn sequence. The claims provide that each peptide comprises a presented turn sequence and a scaffold comprising a first and a second opposite strand with a defined backbone hydrogen binding pattern, wherein the presented turn sequence is flanked by the first and second opposite strands and comprises random amino acids. The specification clearly describes the structural features of the peptide. See the specification, for example, at page 6, lines 1-20. Moreover, Applicants have working examples of at least 9 different species of the peptides in the methods as claimed.

As a matter of clarification, the WX_1W sequence comprises a part of each of the first and second opposing strands of the scaffold.

The Examiner also contends it is unclear which amino acid comprises the presented turn sequence. Applicants submit that the amino acid sequence of the presented turn sequence may

be random, i.e. it is not necessary to identify specific amino acids comprising the presented turn sequence. β-turn sequence are known in the art, and a person of skill in the art would appreciate that the peptide library formed by the claimed methods could be used to stabilize different β-turn sequences. With respect to the term "plurality" and "library", while not acquiescing to the rejection and solely to expedite prosecution, the claim no longer refers to plurality.

For the foregoing reasons, Applicants submit that the claims are not indefinite, and request withdrawal of the rejection.

Rejection under 35 U.S.C. § 103(a)

(a) Cochran et al., WO 00/77194

The Examiner rejected claims 19–27 as obvious over Cochran et al., WO 00/77194). Applicants traverse this rejection.

To make a *prima facie* case of obviousness, there must be (i) a teaching or suggestion in the cited references to modify the references or combine the teachings of the references; (ii) a reasonable expectation of success, and (iii) a teaching or suggestion of all the claim limitations on a cited reference, or combination of reference. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The Examiner has the burden to establish a prima facie case of obviousness.

Applicants submit that these requirements for a *prima facie* case have not been met, because the Cochran reference does not teach or suggest all the claim limitations, nor is there a reasonable expectation of success of modifying the teachings of Cochran to arrive at the presently claimed methods. The Examiner contends that the Cochran reference suggests a method of making a library of peptides containing W-W cross-strands, and therefore, it would be within the ordinary skill in the art to pick and choose specific residues as claimed. Applicants respectfully disagree.

Applicants' claim 19 is directed to a method of constructing a library of peptides, wherein each peptide comprises a presented turn sequence and a scaffold, the scaffold comprising a first and second opposing strand that each comprise a trpzip domain consisting of sequence WX_1W, wherein X_1 is independently threonine, histidine, valine, isoleucine, phenylalanine, tyrosine or tryptophan and the tryptophans form cross strand pairs without a disulfide bond.

Applicants contend that Cochran does not disclose all of the elements of Applicants' claims. Cochran discloses a peptide constrained with a disulfide bond which contributes to the stability of the turn sequence. Moreover, Cochran et al. does not disclose a trpzip domain WX_1W in each of first and second opposite strands. Cochran does not disclose two trp residues separated by one amino acid in each of the first and second opposing strands. Cochran discloses two paired positions A1/A5 and A2/A4 on either side of A3 position. Thus, Applicants submit Cochran et al. does not disclose all of the elements of Applicants' claims.

Moreover, there is no motivation or direction in Cochran to modify the peptide to obtain the peptides made by the method of Applicants. Cochran does not teach or suggest that peptides without a disulfide bond and/or with one trp-trp pair would stabilize a turn sequence. The fact that the art indicated that it was thought that disulfide bonds would not form does not teach anything about whether sequences lacking disulfide bonds were able to stabilize a turn sequence. There is no teaching or suggestion that two trp-trp cross strand pairs formed between a sequence WX_1W in each of the first and second opposing strands would be able to stabilize turn sequences in the absence of a disulfide bond. In addition, the peptides in the method of Applicants have two tryptophan residues separated by another residue. There is no teach or suggestion of this relationship in Cochran. Thus, Applicants submit that there is no teaching in Cochran et al. that would lead one of skill in the art to modify the peptides of Cochran as claimed in the methods of Applicants.

In addition, Applicants would like to point out that all of the experiments in Cochran were conducted with peptides having the disulfide bond. Applicants request that the Examiner clarify that statement on page 5 which seems to suggest that Cochran discloses peptide sequences without the presence of cys.

Applicants disagree with the Examiner with respect to the characterization of the method claims. The method is directed to making a library of peptides, wherein the peptides have certain structural features. There is no teaching or suggestion in Cochran of making a library of peptides having the structural features as claimed by Applicants.

(b) Robinson et al., US 6,878,804 in view of Floudas et al., US 2003/0036093

Claims 19–27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Robinson et al. (US 6,878,804) in view of Floudas et al. (US 2003/0036093). Applicants traverse this rejection.

The Examiner contends that the Robinson reference teaches a method for constructing a peptide library of structurally constrained peptides, and that large surface protein interfaces contain hotspots of binding energy enriched in Trp, Tyr, and Arg. The Examiner admits that the Robinson reference does not teach a trpzip domain (i.e. a Trp-Trp cross-strand zipper-like motif), but cites the Floudas reference as providing motivation to use Trp-Trp cross-strand zipper-like motifs with the methods taught in the Robinson reference. Applicants respectfully disagree.

The Robinson reference is directed to formation of libraries of template-fixed β-hairpin loop mimetics. The structural constraint in the disclosed β-hairpin loop structures arises from fixation of amino acid residues to a functionalized solid support acting as a template (*see* col. 10, line 50 to col. 11, line 16). There is, however, no disclosure in this reference for generating structurally constrained peptides using Trp-Trp cross-strands in a zipper-like conformation. There is also no teaching or disclosure of a scaffold with first and second opposite strands comprising a trpzip domain. Consequently, the Robinson reference provides no teaching or suggestion of a method to generate a structurally constrained peptide with Trp-Trp cross-strands as recited in the present claims. There is no motivation in the reference to substitute the disclosed template-fixation method with a zipper-like Trp-Trp cross-strand motif.

The Examiner indicates that the Robinson reference teaches that dimer interfaces within the hotspots of binding energy can be Trp. However, the reference still does not disclose Trp-Trp cross-strands in a zipper-like motif. Indeed, the Examiner expressly admits that the Robinson reference does not teach a zipper-like motif of the Trp residues.

The Examiner cites the Floudas reference to remedy the deficiencies in the Robinson reference. The Floudas reference is directed to method of predicting peptide tertiary structure and discloses various ab initio methods for combining theories of protein folding to predict β-sheet structure. However, the Floudas reference does not teach or suggest a structurally constrained peptide with Trp-Trp cross-strands, nor does the Floudas reference teach a scaffold

comprising first and second opposite strands, where each strand is a trpzip domain with WX_1W sequence.

Furthermore, there is no motivation in the Floudas reference to combine its teachings with those of the Robinson reference to arrive at the presently claimed methods. These references are directed to totally different methods. Robinson is directed to methods for synthesizing template fixed mimetics and Floudas is a method for predicting whether B turn sequences are present in a molecule. These references are classified in totally different classes both in the U.S. and internationally. In addition, they are directed to solving different problems. Thus, Applicants submit one of skill in the art would not be motivated to combine these references.

A *prima facie* case of obviousness has not been made, as the cited references, either alone, or in combination, do not disclose or teach all the limitations of the present claims. Furthermore, no motivation to combine the references has been shown. Therefore, Applicants respectfully submit that the claims are patentable over Robinson and Floudas, and respectfully request withdrawal of the rejection.

Interview Summary

Applicants request an interview with the Examiner upon receipt of these papers.

SUMMARY

Applicants submit that all claims are now in a condition for allowance, and notification to that effect is requested. The Examiner is invited to contact Applicants' representative at the telephone number listed below, if the Examiner believes that doing so will advance prosecution.

Respectfully submitted,

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